Ontology-based collection, representation and analysis of drug-associated neuropathy adverse events

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ABSTRACT

Neuropathy often occurs following drug treatment such as chemotherapy; severe instances of neuropathy can result in cessation of life-saving chemotherapy treatment. To support data representation and analysis of drug-associated neuropathy adverse events (AEs), we developed an Ontology of Drug Neuropathy Adverse Events (ODNAE). ODNAE extends the Ontology of Adverse Events (OAE). Our combinatorial approach identified 215 US FDA-licensed small molecule drugs that induce signs and symptoms of various types of neuropathy. ODNAE imports related drugs from the Drug Ontology (DrON) with their chemical ingredients defined in ChEBI. ODNAE includes 139 drug mechanisms of action from NDF-RT and 186 biological processes represented in the Gene Ontology (GO). In total ODNAE contains 1,579 terms. Our analysis of the ODNAE knowledgebase shows neuropathy-inducing drugs classified under specific molecular entity groups, especially carbon, pnictogen, chalcogen, and heterocyclic compounds. The carbon drug group includes 127 organic chemical drugs. Thirty nine receptor agonist and antagonist terms were identified, including 7 pairs of agonists and antagonists that share targets (e.g., dopamine, serotonin, sex hormone, and steroid receptor). Many drugs regulate neurological system processes (e.g., negative regulation of dopamine or serotonin uptake). SPARQL scripts were used to query the ODNAE ontology knowledgebase. In conclusion, ODNAE is an effective platform for building a drug-induced neuropathy knowledgebase and for analyzing the underlying mechanisms of drug-induced neuropathy. The ODNAE-based methods used in this study can also be extended to other adverse events.

1 INTRODUCTION

The word neuropathy is derived from two parts: "neuro" referring to the nerve and "pathy" indicating disease. Neuropathy refers herein to nerve damaging. The manifestation of neuropathy often includes chronic pain, loss of sensation, paresthesia, dysesthesia, and motor movement disorders [1]. Drug-induced neuropathies are usually uncommon (2-4% of cases in one outpatient neurology setting), but crucial to recognize because intervention can lead to significant improvement or symptom resolution [2]. Typically, chemotherapy drugs cause higher incidence of neuropathy than other drugs. For example, Bortezomib (a drug for cancer treatment) can cause peripheral neuropathy (PN) in >40% patients. Besides affecting patient quality of life, an effective treatment could be discontinued if PN is intolerable. The signs, symptoms and severity of drug-induced neuropathy are related to many variables such as mechanism of drug action, drug dose, and duration of treatment. Drug targets are diverse and include cell bodies in the dorsal root ganglia, ion channels, myelin sheath, and neuronal mitochondria. These neurotoxic targets often overlap with drug therapeutic mechanisms. For example, taxanes, which interfere with cell division and apoptosis by binding to β-tubulin subunits, can disrupt axonal transport in neurons and eventually lead to axonopathy. While therapeutic strategies to alleviate neuropathy exist, a better understanding of pathophysiological mechanisms of the drug-induced neurotoxicity is needed to aid the development of novel chemotherapeutics with a lower neurotoxic profile.

The study of drug-associated neuropathy adverse events (AEs) relies on the use of different ontologies. Biomedical ontologies are sets of terms and relations that represent entities in the scientific world and how they relate to each other. Ontologies have been used in applications such as the establishment of knowledgebase and computer-assisted automated reasoning. The Ontology of Adverse Events (OAE; http://www.oae-ontology.org/) is a community-based biomedical ontology in the domain of adverse events [3]. OAE provides a logically defined terminology and term relations for various adverse events, including different types of neuropathy adverse events. Drug Ontology (DrON) is a newly generated ontology of drugs and related drug information [4]. DrON incorporates drug information from RxNorm, a normalized drug naming system provided by the National Library of Medicine at NIH [5]. DrON also links drugs to chemical names based on chemical nomenclature as represented in Chemical Entities of Biological Interest (ChEBI) [6]. NDF-RT is another ontology that includes mechanisms of action information of drugs. The mechanisms of actions may be linked to Biological Processes, a part of the Gene Ontology (GO) [7]. All these ontologies provide the basis for interdisciplinary study, representation, and analysis of neuropathy adverse events.

By integrating these ontologies with known drug-associated neuropathy AEs, it is possible to generate a do-

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main-specific ontology to represent and study drug-associated neuropathy AEs. In this paper, we report our efforts in developing a community-driven Ontology of Drug Neuropathy Adverse Events (ODNAE). We collected neuropathy-inducing drugs from a number of datasets, ontologically represented the drugs and their mechanisms, and generated scientific insights using ontology-based approaches.

2 METHODS

Identification of FDA-approved drugs with neuropathy in their labels

Several methods were applied to identify the US Food and Drug Administration (FDA)-approved drugs known to cause neuropathy. First, our study included a list of neuropathy-associated drugs identified from a previous study using literature mining, survey of three databases (Drugs@FDA, DailyMed, and SIDER), and manual curation [8]. This study uses neuropathy related terms from CTCAE [9] and MedDRA [10]. Secondly, we used an ADEpedia dataset developed at Mayo Clinic (http://adepedia.org) [11] to obtain the information on drugs associated with neuropathy. In the ADEpedia dataset, drugs are represented using the RxNorm codes (i.e., RxCUIs) and AEs are represented using the SNOMED CT [12] codes. Thirdly, we searched LinkedSPLs, a Linked Data resource that published the information of FDA-approved drug package inserts from DailyMed [13]. Lastly, we manually reviewed all the package insert documents and selected drugs after manual confirmation.

ODNAE editing and existing ontology term import

ODNAE was developed using the format of W3C standard Web Ontology Language (OWL2) (http://www.w3.org/TR/owl-guide/). For efficient editing of OAE, Protégé 4.3 or 5.0 OWL ontology editor (http://protege.stanford.edu/) was used. Based on the annotated data, we used OntoFox (http://ontofox.hegroup.org/) [14] to extract subsets of related terms from different ontologies. Neuropathy AEs from OAE and drugs from DrON, were retrieved and imported to ODNAE respectively. The mechanisms of most of these drugs are extracted from NDF-RT and imported to ODNAE. Gene Ontology (GO) biological processing terms that match the drug mechanisms were manually identified and imported to ODNAE using OntoFox. Given that many terms from multiple ontologies (OAE, DrON, NDF-RT, and GO) were imported into ODNAE, the alignment of all the imported terms was a challenge and had been solved by a carefully designed strategy to manually assert top level terms of these imported ontology subsets under the ODNAE ontology hierarchical structure. Once the top level terms are aligned, the middle and bottom level ontology terms will be aligned automatically. In addition, we used Ontorat, another internally developed web-based program (http://ontorat.hegroup.org/) [15], to assign RxNorm and NDF-RT identifiers to corresponding DrON drug terms using the annotation property *rdfs:seeAlso*.

Generation of new ODNAE terms and axioms related to drug-induced neuropathy AEs

Ontorat was used to generate specific drug-induced neuropathy AE terms with "ODNAE_" prefix, and define new axioms to link the newly generated ODNAE terms with corresponding drugs and neuropathy AEs. To run the Ontorat program, all the related data were formalized into a structure Excel template. Ontorat scripts were developed to identify sets of data and insert them into ODNAE under appropriate hierarchical structures.

ODNAE access, visualization, and licensing

The ODNAE project website is located at Github: https://github.com/odnae. ODNAE has been deposited in the repositories of Ontobee (http://www.ontobee.org/browser/index.php?o=ODNAE) and NCBO BioPortal (http://bioportal.bioontology.org/ontologies/ODNAE). The ODNAE source code is also freely available under the Creative Commons 3.0 License (http://creativecommons.org/licenses/by/3.0/). This licensing allows ODNAE users to freely distribute and use ODNAE.

SPARQL query of ODNAE

The Ontobee [16] SPARQL query web page (http://www.ontobee.org/sparql) was used to perform SPARQL queries of the ODNAE ontology to answer specifically designed questions.

Heatmap analysis of ODNAE data

The correlation between drug molecular entities and adverse events were presented using a heatmap. The heatmap was created using n×m count matrix, where n is the number of AEs and m is the number of drug molecular entities. The heatmap was ordered using the Manhattan distance and the molecular entities were clustered using the complete linkage method. The heatmap was plotted using R 3.1.3.

3 RESULTS

The overall goal of this project is to generate and analyze an ontology-based knowledgebase of drug-associated neuropathy AEs. To achieve this goal, we first used different methods to identify drugs associated with different types of neuropathy AEs. Related information was then represented in the ODNAE and further analyzed.

In what follows, single quotation marks ' ' are used to quote specific ontology terms.

3.1 215 FDA-licensed drugs were found to be associated with neuropathy adverse events

Using the approach described in the Methods section, we identified 215 chemical drugs known to induce neuropathy

AEs. This list of drugs does not include 36 drugs that were identified from our data sources due to either a lack of DrON IDs, a clear label of a neuropathy AE, or absence of a subclass of neuropathy AE. It is noted that the data from user-reported FDA adverse event case reporting systems (FAERS) [17] were not used. An Excel file containing 215 annotated drugs and neuropathy AEs is stored in the ODNAE Github repository: https://github.com/odnae/odnae/raw/master/src/ontology/Ontorat_inputs/odnae-data-outputupdate.xlsx.

3.2 General ODNAE design and statistics

The top level hierarchy of ODNAE is demonstrated in Fig. 1 and explained below.

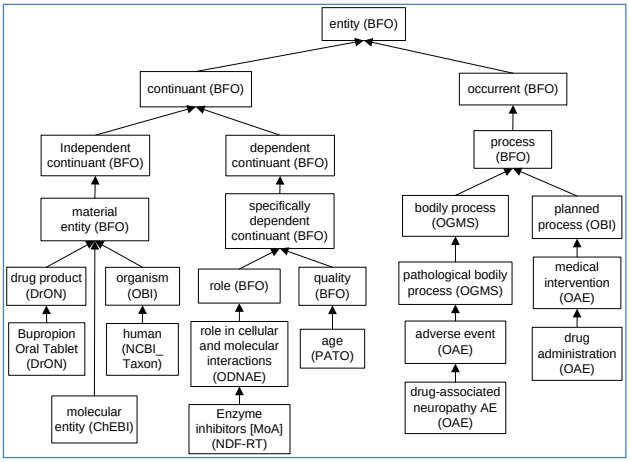

Fig. 1. Top level ODNAE hierarchy.

First, ODNAE extends OAE and reuses the upper level of OAE. Like OAE, ODNAE uses the Basic Formal Ontology (BFO) [18] as the upper level ontology. BFO contains two branches, 'continuant' and 'occurrent' [19, 20]. The 'continuant' branch represents time-independent entities such as material entity and quality. The 'occurrent' branch represents time-related entities such as adverse event, drug administration, drug metabolism, and dose accumulation in human. By aligning different terms under the two branches of BFO, knowledge from broad biological areas related to drug-associated neuropathy AEs were captured and organized under a comprehensive ontology-level structure.

Among several drug ontologies (RxNorm, NDF-RT, and DrON), we selected DrON as the default ontology for representing drugs, as DrON allows mapping between drugs and ChEBI chemical terms. In addition, like ODNAE and OAE, DrON is also aligned with BFO. The advantage of using BFO is that BFO has been adopted by over 100 biomedical ontologies. All these ontologies follow ontology design principles of the Open Biomedical Ontologies (OBO) Foundry [20]. Therefore, we were able to easily import and integrate related terms from DrON, OAE, and other OBO ontologies into ODNAE. In order to enable data integration and data reuse, we added links from the DrON terms to RxNorm and NDF-RT IDs by annotation property *rdfs:seeAlso* in ODNAE .

Fig. 2 shows the basic design pattern of ODNAE representation of drug-associated neuropathy AEs (Fig. 2A) and one example of implementing the design (Fig. 2B). Specifically, a 'drug-associated neuropathy AE' (*e.g.*, 'bupropion-associated neuropathy AE') occurs after ('preceded_by') an administration of a drug (*e.g.*, Bupropion Oral Tablet or Aplezin) in a 'human' patient. The human has different qualities (such as 'age', 'gender', and 'disease history') and genomics background which may affect adverse event outcomes. The drug has a proper component of a molecular entity (*e.g.*, bupropion). The drug also has a specific role in a biological process. The NDF-RT mechanism of action (MoA) terms (*e.g.*, dopamine uptake inhibitor) is represented as 'role' (BFO_0000023), which is realized in a Gene Ontology (GO) biological process (*e.g.*, 'negative regulation of dopamine uptake' GO_0051585) (Fig. 2).

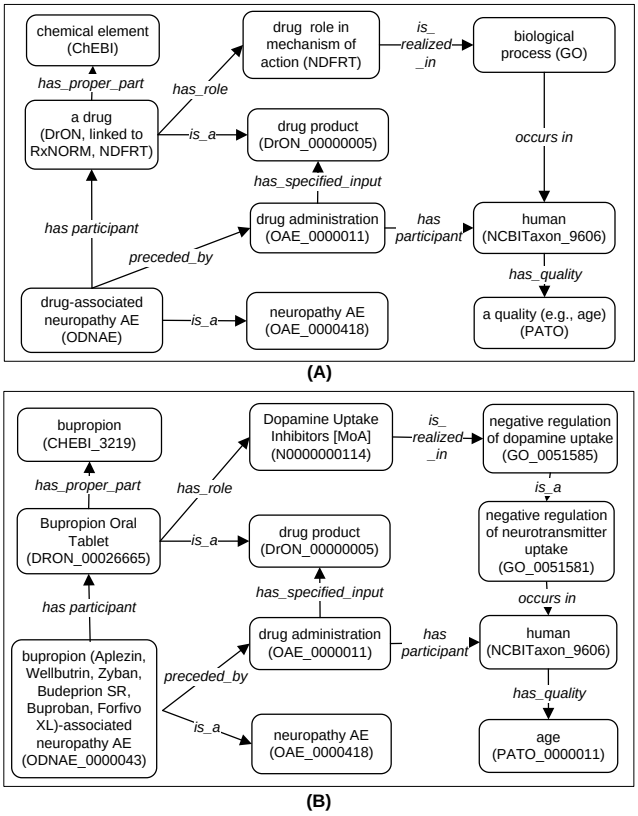

Fig. 2. ODNAE design pattern and example. (A) ODNAE design pattern of representing drug-associated neuropathy AE. (B) ODNAE representing bupropion-associated neuropathy AE.

The linked information illustrated in Fig.2 is logically defined in ODNAE. Logical constraints allow proper integration and hierarchies among terms from different ontologies of drugs, the chemicals of active drug ingredients, GO processes, and other information cross-linked with axioms. As a result, the ontology knowledgebase of drug neuropathy AEs can be analyzed at different levels of classification.

As shown in Fig. 1 and 2, ODNAE imports terms from many existing ontologies and also contains newly generated, ODNAE-specific terms. In total, ODNAE contains 1,579 terms, including 249 terms with "ODNAE_" prefix and terms imported from other ontologies such as 25 OAE terms, 500 ChEBI terms, and 331 DrON terms. The detailed statistics of ODNAE is available at the Ontobee website: http://www.ontobee.org/ontostat.php?ontology=ODNAE.

In the next sections, we will provide more details about the ODNAE contents and scientific insights from ODNAE data analysis.

3.3 Various types of neuropathy AEs are associated with drugs

Our study identified 20 types of neuropathy AEs, each of which is associated with at least one drug (Fig. 3). Represented in a hierarchical structure, these AEs are logically defined and cross-referenced to existing AE representation systems including MedDRA [10].

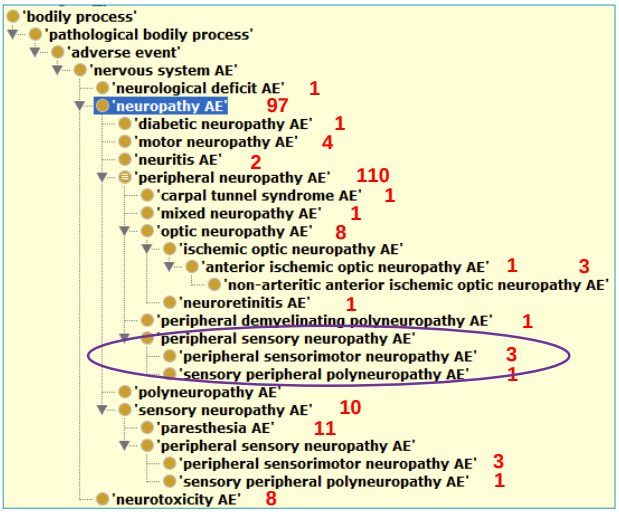

Fig. 3. Various drug-associated neuropathy AEs as represented in OAE and imported to ODNAE. Red numbers represent the numbers of drugs associated with the corresponding AEs. Circled are 3 terms not asserted but inferred under 'peripheral neuropathy AE' using a Hermit reasoner in Protege OWL editor.

3.4 Ontology representation of neuropathy-associated drugs and drug ingredients

The active ingredient of a drug product plays a vital role in its mechanism. The chemical structures of the drug active ingredients are represented in ODNAE using ChEBI terms. Additional ChEBI terms are also imported to form the hierarchy of these active ingredients of drugs. The relation between a drug and a ChEBI chemical is presented by an object property 'has_proper_part' (Fig. 2).

Most drug-associating ChEBI terms are under the branch of 'molecular entity' (CHEBI_23367). There are 23 classes, for example, 'carbon group molecular entity' (CHEBI_33582), at the third layer below ChEBI term 'molecular entity' (Fig. 4A). Among all these 23 classes, the carbon group molecular entity class is associated with 127 drugs (the highest number). All drugs under this group were indeed all organic molecular entities (Fig. 4A). Among 13 subclasses of organic entities, heterorganic entities link to 116 neuropathy-inducing drugs (Fig. 4A). Fig. 4B provides an example of a subclass of heterorganic entities (Fig. 4B). All the results can be counted from the ontology display in the Protégé OWL editor. Alternatively, as detailed later, a SPARQL script can obtain the same count results.

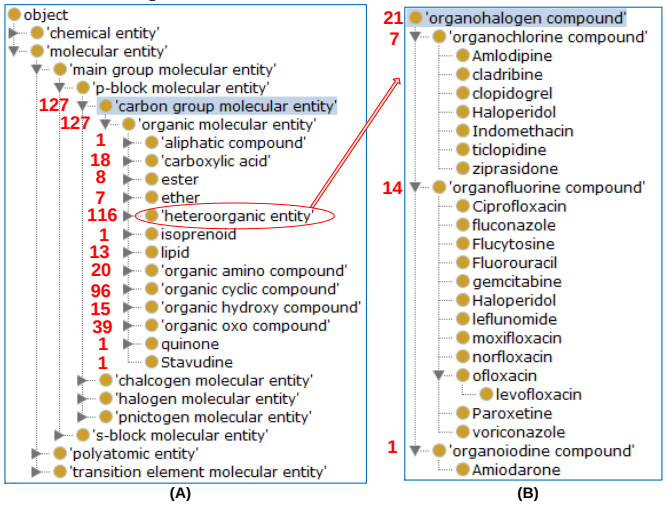

Fig. 4. Example ChEBI classification of drug chemicals inducing neuropathy AEs. (A) 14 neuropathy-inducing drugs are classified under nucleotide. (B) 21 drugs containing organohalogen compounds as active ingredients were found to induce neuropathy AEs.

3.5 Ontology-based representation and analysis of drug mechanisms

A total of 139 mechanisms of action (MoA) terms related to neuropathy-inducing drugs was identified from NDF-RT and imported to ODNAE. We identified 13 GO biological processes that directly realize roles, or MoAs from NDF-RT. Many MoA terms do not have matched GO terms. ODNAE also includes 173 GO terms that are the ancestor (or related) terms of these 13 GO terms.

Much insight was gained by examining the NDF-RT MoAs collected in ODNAE (Fig. 5). All NDF-RT roles were organized as subclasses of 'role in cellular and molecular interactions', including the roles as enzyme inhibitors, immunological and biological factors, and receptors of different biological interactions. Our results showed that 12 neuropathy AE related drugs inhibit the uptake of three neurotransmitters [dopamine (1), norepinephrine (10), and serotonin (11)]. There are 20 drugs that interact with the G-protein receptors that contribute to neuropathy adverse events. We identified 39 drug agonist and antagonist terms, including 16 agonists and 23 antagonists. Among them, there are 7 pairs of agonists and antagonists that share targets, including adrenergic, dopamine, and steroid hormone receptor agonists/antagonists shown in Fig. 5. The other four pairs are sex hormone, serotonin, hormone, and adrenergic alpha agonists/antagonists.

The GO terms in ODNAE cover a variety of processes, including negative regulation of neurotransmitter uptake and synaptic transmission. GO terms are linked to genes and proteins. We will investigate in the future how ODNAE can represent gene/protein-based neuropathy mechanisms with the support of GO.

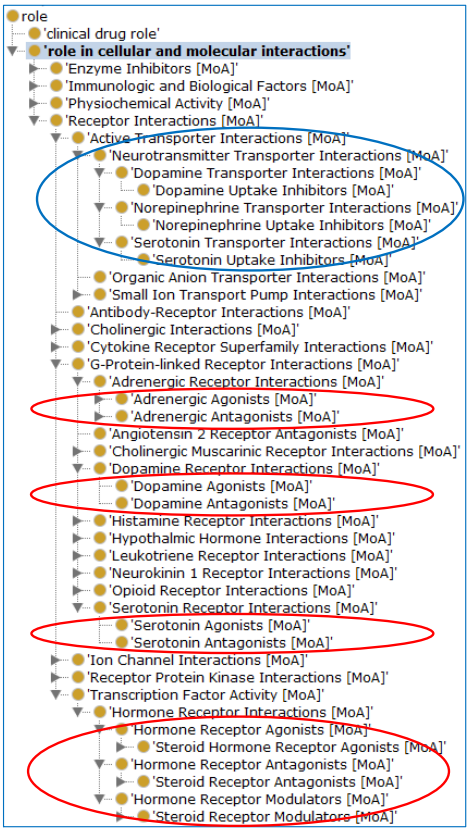

Fig. 5. Various roles in cellular and molecular interactions played by drugs associated with neuropathy AEs. The branch circled in blue indicates inhibitor roles related to neurotransmission. Roles circled in red indicate either agonists or antagonists associated with neuropathy AEs.

3.6 Query of drug-induced neuropathy AEs

The ODNAE knowledgebase can be queried through the Ontobee SPARQL program. Different questions can be addressed using SPARQL queries. For example, a SPARQL script was generated to identify what drugs act as a serotonin agonist (Fig. 6). The query resulted in three drugs: eletriptan, almotriptan, and zolmitriptan. Using the same approach, we also found one drug (ziprasidone Oral Capsule) that acts as a serotonin antagonist (N0000000130).

```
#Goal: Find drugs has_role (RO_0000087) of
#       Serotonin Agonists [MoA] (N0000000256) from ODNAE
prefix owl: <http://www.w3.org/2002/07/owl#>
prefix obo: <http://purl.obolibrary.org/obo/>
prefix ndfrt: <http://evs.nci.nih.gov/ftp1/NDF-RT/NDF-RT.owl#>
SELECT distinct ?drug ?drug_label
FROM <http://purl.obolibrary.org/obo/merged/ODNAE>
WHERE {
  ?drug rdfs:subClassOf ?bnode .
  ?drug rdfs:label ?drug_label .
  ?bnode owl:onProperty obo:RO_0000087;
                owl:someValuesFrom ndfrt:N0000000256 .
}
```

Output format: Table Max Rows: 10

Run Query Reset

Result | Raw Request/Permalinks | Raw Response

drug	drug_label
http://purl.obolibrary.org/obo/DRON_00013763	eletriptan
http://purl.obolibrary.org/obo/DRON_00018348	almotriptan
http://purl.obolibrary.org/obo/DRON_00023808	zolmitriptan Oral Tablet

Fig. 6. SPARQL query of drugs acting as a serotonin agonist. The query was done in Ontobee SPARQL website (http://www.ontobee.org/sparql).

3.7 Heatmap analysis of the correlations between drug molecular entities and neuropathy AEs

Using the SPARQL queried results, we performed various analyses. For example, we generated SPARQL scripts to obtain the drug molecular entities and AEs that are associated with different drugs in ODNAE. Such data were further used to generate a heatmap to explore the correlation between drug molecular entities and various neuropathy AEs (Fig. 7). Our results showed that drug-associated carbon groups (CHEBI_33582), pnictogen (CHEBI_33302), chalcogen (CHEBI_33304) and heterocyclic compounds (CHEBI_5686) were associated with the highest numbers of AE cases (Fig. 7).

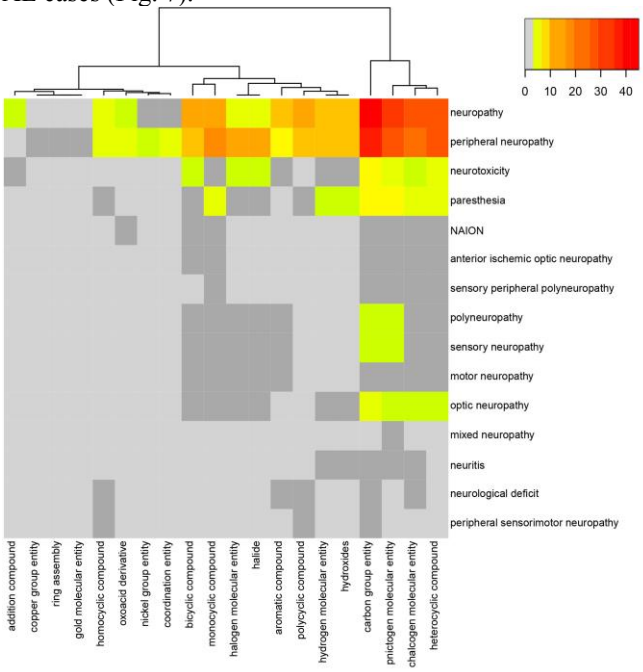

Fig. 7. Heatmap analysis of drug molecular entity-AE relations. Drug molecular entities covered DrON terms at the third layer

under the ChEBI term 'molecular entity'. Light grey is 0 and dark grey is the 1. The rest are ordered by yellow, orange and red.

4 DISCUSSION

Drugs of diverse pharmacological classes may cause symptoms and varying degrees of severity of neuropathy AEs. Systematic classification and analysis of these drugs are crucial in finding common features and mechanisms of how they cause neuropathy. Biomedical ontologies provide an ideal platform for integrating and analyzing related information. In this study, we generated ODNAE to represent drug-induced neuropathy AEs and link these AEs to different sets of data (*e.g.*, drugs, chemical characteristics, drug targets, roles, and biological processes). The patterns of neuropathy AE related drugs were analyzed, which provides the basis for further analysis of the inherent mechanisms of drug-induced neuropathy AEs.

As a knowledgebase, ODNAE captures knowledge extracted from biomedical bench research, clinical practices, and public health. Owing to the parsable and machine readable nature of the AE knowledgebase, ODNAE supports neuropathy AE data exchange, data integration, and automated reasoning and classification. The scientific findings from this study demonstrate the advantage of ontology supported data integration and classification, which benefits downstream statistics analysis. The OAE/ODNAE-based framework can be extended to other drug and AE studies.

Chemical characteristics of drug, drug disposition in humans, and patient factors could all play a role in the induction of adverse drug events. For example, age, drug dosage, and individual patient biology each play a critical role in specific drug neuropathy AEs. As shown in Fig. 2, these parameters can be linked to other elements presented in a semantic framework. The ODNAE-based integrative analysis would be able to identify relations between those factors and drug-associated neuropathy. Our work defines a very important framework for understanding drug-induced peripheral neuropathy. Ultimately it will allow us to advance personalized medicine, including the development of neuroprotective strategies for cancer patients or patients suffering from neurological disorders such as diabetic neuropathy.

Our ONDAE will be continuously expanded and computerized to integrate multiple layers of information, including chemical characteristics of drugs, biological receptors and processes at the cellular level, drug disposition in patients, pharmacogenetics, and population level variables.

5 CONCLUSION

ODNAE is a biomedical ontology and a knowledgebase of neuropathy AEs associated with 215 drugs. The analyses of logically formed ODNAE information revealed scientific insights into drug-associated neuropathy adverse events.

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DISCLAIMER

The views expressed are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US Food and Drug Administration or the US government.

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